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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,097	02/13/2002	Nnochiri N. Ekwuribe	9233-46	7253

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EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,097	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Andrew D Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114-169 and 208-217* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-169 and 208-217* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/26/03, 1/13/03, *.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: **1/23/04*.

DETAILED ACTION

Applicant's election without traverse of Group V in the reply filed on July 27, 2004 is acknowledged.

Applicant's amending of Group VI to depend from Group V, is acknowledged. Groups I-IV and VII are cancelled by said amendment.

Claims 114-169 and 208-217 are pending.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicant elected the species:

Insulin polypeptide-N(H)C(O)$(CH_2)_5(OCH_2CH_2)_7OCH_3$. This species is identified in the specification as HIM2 (page 32).

Examiner Notes

Herein, citations to relevant passages of U.S. Patents are as (Column #: line #), i.e.- (c3:1+). For foreign patents and non-patent literature it is as (Page #), i.e.- (p1), and when applicable (Page #: line or paragraph #), i.e.- (p1:4 or p1:p4).

Information Disclosure Statement

The information disclosure statements filed (A) November 26, 2003 and (B) January 13, 2003 fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Regarding:
(A): 7 has not been considered as it is the PGPUB of the instant application.
35, 36, 56, and 57 have not been considered as no copies of the references have been provided.

(B): 82 has not been considered as it is a duplicate reference which has been considered on (A).

139-201 have not been considered as no copy of the references have been provided.

Specification

The specification is objected to for the following informalities:

Pages 33 and 34 recite, "...Serial No. _____" without having the number present.

Appropriate correction is required.

Claim Objections

Claims 128 and 156 are objected to for improper claim language. Claims 128 and 156 recite Markush groups, however the species are not presented in the alternative. Appropriate claim language recites either "selected from A, B, or C" or "selected from the group consisting of A, B, and C".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 142-169, and 208-217 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 208-212 recite the limitation "the amphiphilically-balanced". There is insufficient antecedent basis for this limitation in the claims.

Claims 142 and claims 213-215 are confusing and therefore indefinite.

Claim 142 recites, "The method of claim 114 [A method of treating diabetes mellitus in a patient in need of such treatment], wherein the orally administering ... to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient ..." It is unclear whether the meal is ingested to treat diabetes, or whether the oligomer is administered to treat diabetes, and is administered near a meal time.

Claim 213-215 and 217 recite, "The method of claim ... wherein the insulin ... conjugate comprising the structure... , ." Because of the "wherein" and claim ending in ", .", it appears as if further limitations on the method are omitted. For example, Applicant may have intended to recite, wherein the oligomer comprising IV "is administered orally", or "is administered to a patient", or "is administered in a pharmaceutical composition". Alternatively, Applicant may have intended the claims to recite simply wherein the administered compound comprises the structure of Formula IV.

Claims 143-169 and 216 are rejected as being directly, or indirectly, dependent from a rejected claim, and for failing to correct the deficiency.

Claim Rejections - 35 USC § 102

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 114-122, 126, 127, 129-150, 154, 155, 157-169, and 208-217 are rejected under 35 U.S.C. 102(a) as being anticipated by Allaudeen, *et al.*[a]

The instant claims are drawn to methods of treating diabetes with oral insulin, formed as an insulin-oligomer. One such embodiment is the species elected, *supra*, identified in the specification as HIM2.

Allaudeen teaches the hexyl insulin conjugate 'M2' which was purified and "tested for oral activity in the pancreatectomized dog model." It is the Examiner's position that purification of HIM2 from HID2 or HIM1 results in a 'monodispersed' mixture.

It is the Examiner's position that, absent evidence to the contrary, HIM2 is hexyl insulin conjugate M2.

The dose administered in Allaudeen, 1 mg/kg, is identical to that in Example 1 of the instant application (p42). As such, any pharmacokinetic and/or pharmacodynamic physiologic effects elicited *in vivo* are inherent to the compound.

Because Allaudeen teaches HIM2 administered to dogs at 1mg/kg, Claims 114-122, 126, 127, 129-150, 154, 155, 157-169, and 208-217 are anticipated.

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[a] Reference 38, PTO-1449 11/26/2003.

Claims 114-122, 126, 127, 129-150, 154, 155, 157-169, and 208-217 are rejected under 35 U.S.C. 102(b) as being anticipated by Radhakrishnan, *et al.*[b]

The instant claims are presented *supra*.

Radhakrishnan teaches that "the orally activity of M2 was studied in a microemulsion formulation in [the] pancreatectomized dog model." It is further taught that, "M2 is orally active in pancreatectomized dogs at doses as low as 0.3 mg/kg."

It is the Examiner's position that, absent evidence to the contrary, that M2 is HIM2.

Because Radhakrishnan teaches M2 administered to dogs at doses as low as 0.3 mg/kg, Claims 114-122, 126, 127, 129-150, 154, 155, 157-169, and 208-217 are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 114-127, 129-155, 156-169, and 208-217 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allaudeen or Radhakrishnan, each as applied *supra*.

The instant claims are presented *supra*. Allaudeen and Radhakrishnan do not teach the specific administration as pre-, contemporaneously, or post- meal.

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[b] Reference 65, PTO-1449 11/26/2003.

It would have been obvious to one skilled in the art at the time of invention to determine all operable and optimum dose regimens, such as time of administration relative to a meal, with the claimed composition of because scheduling of dose administration is an art-recognized result-effective variable that is routinely determined and optimized in the medicinal arts, specifically the diabetes/insulin arts.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 114-169 and 208-217 rejected under 35 U.S.C. 103(a) as being unpatentable over view of Allaudeen or Radhakrishnan, each as applied *supra*, in view of Vajo and Duckworth[c].

The instant claims are presented *supra*. The instant claims are further drawn to insulin analogs wherein residues are modified.

Allaudeen and Radharkrishnan are presented *supra*. Neither reference teaches the use of specific insulin amino acid substituted analogs, referring only to the generic term "insulin".

Vajo teaches that, "[s]ubstitution of AsnB3 by Gln, and AsnA21 by Ala or Gly results in analogs with 30 times less deamination and 10 times reduced formation of covalent dimers." (p6, citing- *J Brange (1997) The new era of biotech insulin analogs.*

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[c] Z Vajo and WC Duckworth, Pharm. Rev. (2000) 52, 1-9.

Diabetologia 40:S48-s53.). Vajo also teaches that LISPRO, wherein Lys28 and Pro29 are the reverse of the 'normal' Pro28 and Lys29, "causes a decreased tendency for self-association, and as a result, faster absorption, higher peak serum levels, and shorter duration of action...[relative] to regular insulin." (p3, citing *DC Howey, et al. (1994) [Lys(B28),Pro(B29)]-human insulin: a rapidly absorbed analog of human insulin. Diabetes, 43, 396-402.*). Vajo further teaches that the reversal of amino acids in LISPRO, "do not affect its receptor-binding domain. Therefore, the affinity to the insulin receptor of insulin LISPRO is similar to that of regular insulin..." (p3).

Vajo is relied upon for the reasons discussed above. If not expressly taught by Allaudeen or Radharkrishnan, based upon the overall beneficial teaching provided by Vajo with respect to the effect of amino acid substitutions in insulin in the manner disclosed therein, the selection of a modified insuln with specific characteristics, such as, but not limited to, reduced duration of action, faster absorption, and reduced self association, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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